CADTH

**CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL**

Osseointegrated Prosthetic Implants for Lower Limb Amputation: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	February 27, 2017
Report Length:	42 Pages

Authors: Kellee Kaulback, Alison Jones

Cite As:. Osseointegrated prosthetic implants for lower limb amputation: a review of clinical effectiveness, cost-effectiveness and guidelines. Ottawa: CADTH; 2017 Mar. (CADTH rapid response report: summary with critical appraisal).

Acknowledgments:

ISSN: 1922-8147 (online)

Context and Policy Issues

Lower limb amputation is most commonly due to vascular problems, followed by traumatic events, tumours, and infections.[1] Major (non-toe) lower limb loss was estimated at 623,000 cases in the United States in 2005, of which 81% were due to dysvascular causes, 17% were due to trauma, and 2% were due to cancer.[2] Between 2006 and 2008, 5342 patients in Canadian hospitals underwent non-traumatic lower-extremity amputations, most frequently after admission for diabetic complications (81%), cardiovascular disease (6%), or cancer (3%).[3]

About 86% of people with a major lower extremity amputation are fitted with a socket prosthesis.[4] The conventional socket prostheses rely on suction or strapping of the prosthesis to the residual limb.[5] Between 34% to 63% of socket prosthesis users have chronic skin problems and pain resulting from friction between the residual limb and the prosthesis.[4] Pressure sores, dermatitis, neuromas, bony overgrowth, fistula formation, ischial irritation, hyperhidrosis, itching, acne, and scrotal lacerations have been reported with socket prosthesis use.[1] These problems can have a severe impact on quality of life, activity level, and limitations in participation level.[4] One study has reported that among 78 socket prosthesis users, 29% could ambulate outdoors, 46% were non-ambulatory, with as few as 42% used their prosthetic limbs.[1] Some patients may be unable to use a socket prosthesis at all due to a short residual limb, skin grafts, scarring, or heterotopic bone formation.[6]

Over the last two decades, osseointegration has emerged as an alternative to the socket prosthesis.[7] Osseointegration refers to the structural and functional connection between the surface of a biocompatible metal implant and living bone.[7] An osseointegrated prosthesis (OIP) eliminates the problem interface between the socket prosthesis and the residual limb by attaching the prosthesis directly to the bone in the residual limb.[7] In addition to eliminating socket-related issues, one of the other benefits attributed to OIP is improved osseoperception, that is, the ability to perceive pressure, load, position, and balance.[4] Other benefits of OIP that have been reported include direct prosthesis control, improved stability, better fixation, maximum sitting comfort, larger hip range of motion, quick donning and doffing, improved body perception, increased walking ability, improved functional capacity, and an overall increase in quality of life.[8] The OIP is also referred to as a bone-anchored prosthesis or direct skeletal fixation of an intraosseous transcutaneous implant.

While there are variations depending on protocol and implant type, the OIP procedure is carried out in in two stages that can be performed over two separate operations, or can be done sequentially in a single operation.[9] In the first stage, a metal rod is inserted into the bone of the residual limb, and if the procedure is being performed in two stages, the residual limb wound is then completely closed and allowed to heal.[9] In the second stage, either during the same operation or after a period of time has elapsed (allowing osseointegration to take place), the implant is surgically re-exposed, and connected to a small metal extension, known as an abutment.[9] With the abutment penetrating the skin, the wound is closed, allowing attachment of the external prosthesis to the intraosseous implant. A period of rehabilitation follows, during which time a training prosthesis is used.[9] Successful osseointegration between the implant and the bone is essential for both stability and protection from infection.[1] As the design of the OIP requires that the implant protrude through the skin to allow for direct connection to the prosthesis, there is potential for eventual bacterial colonization at the prosthesis-skin interface (stoma) and bacteria tracking up the metal implant to the femur.[10] An OIP procedure is generally an option only when the cause of amputation is trauma or cancer, and is currently not indicated for patients whose amputation was due to a vascular cause due to a higher risk of infection in these patients.[4] Current practice patterns and policy across the different jurisdictions offering OIP require that a patient must be experiencing socket-related problems to qualify for an OIP.[4]

There are several different OIPs available, including the Osseointegrated Prosthesis for the Rehabilitation of Amputees (OPRA), the Endo-Exo Femoral Prosthesis (EEFP) (now known as the Integral Leg Prosthesis, or ILP), the Osseointegration Group of Australia-Osseointegration Prosthetic Limb (OPL or OGAP-OPL) and the Intraosseous Transcutaneous Amputation Prosthesis (ITAP).[1,5,9] Each OIP is characterized by different types of implants in terms of materials and design, different methods of skin integration, and different surgical and rehabilitation protocols.

The Osseointegrated Prosthesis for the Rehabilitation of Amputees (OPRA) is the most established of the OIP devices, having been in use since 1990.[5] The OPRA OIP uses a titanium screw-fixation implant, and involves two operations that are separated by at least six months.[4] As of 2015, the EEFP, now known as the ILP, has seen three design iterations since its introduction in 1999.[11] The modifications were made to improve clinical outcomes and in particular, to reduce adverse events. The ILP uses a chromium-cobalt-molybdenum alloy implant with an interval between operations of six to eight weeks.[1,4,6] Both the ILP and the OPL use a press-fit design meant to encourage osseous penetration and in-growth rather than a screw-fixation implant, which is thought to encourage bone on-growth (through osseous cancellization).[6,7] The press-fit design is thought to improve long-term implant survival.[6] One study has reported increased peri-prosthetic cortical thickness around the ILP implants in the first 2 years after implantation, indicating good prospects for implant survival and possibilities for potential revision surgery.[12] The OPL is the newest (2013) of the OIP implant devices.[6] It is thought to provide a closer match to the elastic modulus of the bone than the ILP.[6] The OGAP-OPL utilizes a titanium alloy implant, and the procedure usually completes in one operation, or two operations four to eight weeks apart.[5-7,13] The ITAP is implanted in a single operation that is available only in the United Kingdom as part of a pre-CE mark (i.e., exclusively for clinical investigations) clinical study.[1,5] A summary of the different types of OIP implants and procedures for which outcomes have been reported are detailed in Appendix 1.

This Rapid Response seeks to assess the comparative clinical and cost-effectiveness of OIP versus either socket prostheses or no prosthesis, in people with lower limb amputation, as well as identify and review any evidence-based guidance for the procedure.

Research Questions

1. What is the clinical effectiveness of osseointegrated prosthetic implants for patients with lower limb amputation?

2. What is the cost-effectiveness of osseointegrated prosthetic implants for patients with lower limb amputation?
3. What are the evidence-based guidelines regarding the use of osseointegrated prosthetic implants in patients with lower limb amputation?

Key Findings

There is evidence from low-quality studies to support the use of osseointegrated prosthetic implants (OIP) in people with transfemoral amputation. Consistent improvements were demonstrated across the included studies in measures of condition-specific quality of life, general quality of life, and function, for OIP users as compared with socket prosthesis users. Adverse event rates, particularly infection, are common across most studies, and long-term follow-up for most types of OIPs is not available. The available evidence suggests that careful attention should be given to patient selection, implant selection, and residual limb skin integration, as well as surgical and rehabilitation protocols, to optimize outcomes and reduce adverse event rates. Costs for the OIP prosthesis, and services are similar to that of the socket prosthesis based on one study; however, no evidence was identified that evaluated the cost of the implant surgery, hospitalization, medical check-ups, and potential complications.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and January 26, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 2.

Table 1: Selection Criteria

Population	Patients (18 years or older) requiring prosthetic implants after lower limb amputation Subgroups of interest: diabetes or peripheral vascular disease
Intervention	Osseointegrated prosthetic implants for lower limb amputation
Comparator	Socket prosthetic for limb amputation; No prosthetic No comparator (safety only)
Outcomes	**Q1:** Clinical effectiveness (e.g., questionnaire for persons with a transfemoral amputation (Q-TFA),

	prosthetic limb users survey (PLUS-M), patient reported outcomes (e.g., PROMIS), Trinity Amputation and Prosthesis Experience Scales (TAPES), Amputation Mobility Predictor scores (K-levels), survival, quality of life, walking ability [6 minute walk test, timed up and go, L-test, AMP + CHAMP], and functional outcomes [gait analysis, range of motion, ambulation, activity level], pain, length of rehabilitation, frequency of follow-up visits, psychosocial outcomes (e.g., Depression Anxiety Stress Scale [DASS]); Osseoperception/vibratory stimulation (ability to perceive pressure, load, position, balance; Energetic cost of walking Harms (e.g., complications including superficial skin infection, severe infection [deep bone, implant infection], fracture, surgical complications, readmission due to complications or device failure) **Q2:** Cost-effectiveness outcomes (e.g., cost per quality adjusted life year, cost per health benefit gained) **Q3:** Evidence-based guideline recommendations regarding the use of osseointegrated prosthetic implants in patients with lower limb amputation
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCTs), non-RCTs, economic evaluations, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 2, they were duplicate publications, or were published prior to 2007. Articles were also excluded if they were captured within an included systematic review, were case reports, or animal studies.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR[14] and individual clinical studies were assessed using the Downs and Black checklist.[15] Guidelines were assessed with the AGREE II[16] instrument. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described, narratively.

Summary of Evidence

Quantity of Research Available

A total of 111 citations were identified in the literature search. Following screening of titles and abstracts, 91 citations were excluded and 20 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search, and one was identified from the reference list of another publication. Of these potentially relevant articles, 15 publications were excluded for various reasons, while seven publications met the inclusion criteria and were included in this report. Appendix 2 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Detailed study characteristics are presented by study type.

Study Design

Systematic Reviews

Two SRS[1,4] were identified that evaluated the clinical effectiveness of OIP for lower limb amputation. One of the SRs included one cost analysis study.[1] The SRs were published in 2015[1] and 2016.[4] Search dates were from database inception to May 2014 (with a search update prior to manuscript submission),[1] and from a start date not specified (inception assumed) until April 16, 2016 for the other SR[4] One SR[1] included 13 studies, including seven retrospective cohorts, three prospective cohorts, two retrospective comparative studies, and one retrospective cost analysis. The other SR included seven studies, five of which were before-after cohorts, and two that were cross-sectional studies. Details of the included systematic reviews are provided in Table A2, Appendix 3. There was some overlap between the primary studies included in the two SRs (Table A3, Appendix 3). Of the 20 primary studies reviewed, 4 were common to both SRs. Discrepancies in the included studies were due to differences in research questions, included study designs and other selection criteria.

Individual Clinical Studies

Four individual primary studies were identified.[6,7,13,17] One prospective cohort study[13] and one retrospective data analysis[8} reporting clinical outcomes before and after OIP in transfermoral amputees were identified. One two-centre prospective before-after cohort study evaluating the safety of OIP for transfemoral amputees was identified.[7] Finally, one prospective non-randomized study[17] with both a before-after OIP comparison, and a control group comparison, was identified (Table A4, Appendix 3).

Guidelines

One guideline[18] regarding OIP was identified, with an associated evidence overview.[9]

Country of Origin

Systematic Reviews

The SRs were conducted by authors in the Netherlands[4], and the United States[1] (Table A2, Appendix 3).

Individual Clinical Studies

Two of the included primary studies were conducted in Australia[6,13], and one[7] was conducted in two centres, Australia and The Netherlands. One study[17] was conducted in Sweden (Table A4, Appendix 3).

Guidelines

The guideline was produced by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom (Table A5, Appendix 3).

Patient Population

Systematic Reviews

Both SRs included studies evaluating participants with a lower extremity amputation. One of the SRs included at least one study with a mix of participants with upper and lower extremity amputation.[1] One SR[4] reported on a total of 327 participants (142 with an OIP and 185 socket prosthesis users), while the other SR[1] included 540 participants. The age range at OIP implantation was 17 to 78 years,[1] while the other

SR[4] reported the age at study inclusion, ranging from 20 to 70 years. A higher ratio of males to females was reported in nine of 13 studies (sex not reported for three studies) included in one SR,[1] while the other SR reported a higher ratio of males to females receiving the OIP) for four of the seven included studies. In both SRs, the reason for amputation was primarily due to trauma, followed by tumour, and rarely, other indications, including arterial embolus and infection (Table A2, Appendix 3).[1,4]

Individual Clinical Studies

A total of 159 (116 males, 43 females) participants were included across the three studies that primarily evaluated quality of life, function, and adverse events, with either an ILP or OPL implanted between 2009 and 2014.[6,7,13] All three studies included transfemoral amputees that had experienced socket prosthesis-related issues, or were wheelchair bound. In all three studies, trauma was the primary reason for amputation, followed by oncology, infection, congenital, and other causes. None of the studies included participants with dysvascular causes of amputation. The included patients ranged in age from 20 to 81 years. One study[7] included participants with a bilateral amputation, while the other two studies[6,13] included only unilateral amputees. One study[13] reported time from amputation to OIP surgery ranging from less than two years to 65 years, while one study[7] reported that patients has been using a prosthesis for between zero to 63 years prior to the OIP procedure (Table A4, Appendix 3).

The fourth study[17] evaluated detection thresholds of vibrometric stimuli, and included 17 patients (n = 8 males, n = 9 females) in the OIP group, with a mean age of 44.6 years (range 23 to 63 years). The OIP was implanted between 1998 and 2007. The mean time since amputation was 14.5 years (range 2 to 42 years). The cause of amputation was due to trauma in 11 patients, and tumour in six. The control group included 17 patients (n = 11 males, n = 6 females) that were socket prosthesis users, with a mean age of 43.2 years (range 29 to 63 years). The mean time since amputation was 18 years (range 2 to 34 years). The cause of amputation was trauma in 11, and tumour in 6 (Table A4, Appendix 3).

Guidelines

The guidance issued by NICE targeted clinicians wishing to undertake osseointegrated prosthetic procedures (Table A5, Appendix 3).

Interventions and Comparators

Systematic Reviews

One of the SRs[4] evaluated two-step OPRA in six studies, and two-step EEFP in one study. The comparator was socket prosthesis for all included studies, with one cohort study also comparing the participants in the OIP group with healthy controls. In five studies, the before-after cohort design allowed comparison before and after the OIP surgery in former socket prosthesis users, while two studies were cross-sectional with a control group of socket prosthesis users. The other SR[1] evaluated OPRA (two-step) in seven studies, EEFP (two-step) in five studies, and ITAP (one-step) in one study. Only three of the studies were described as comparative, and in each case the comparator was socket prosthesis (Table A2, Appendix 3).

Individual Clinical Studies

In one before-after study,[6] investigators implanted the OPL prosthesis with no interval between stages reported, suggesting the procedure was performed in a single operation. In this study, the comparator was pre-procedure socket prosthesis users (n = 12), and wheelchair-bound participants (n = 10). In another before-after study,[13] participants were implanted with either the ILP or OLP device in two operations with a four to eight week interval between stages, employing the OGAAP-1 protocol for rehabilitation. The comparator was pre-procedure socket users (n = 36) and wheelchair-bound participants (n = 14). The prospective cohort study[7] reporting on adverse events utilized the ILP device in a two-stage surgical procedure with six to eight weeks between the stages, with either the OGAAP-1 or another protocol (not described) followed for rehabilitation. No comparative information was provided. The final study evaluated detection thresholds of vibrometric stimuli in patients with transfemoral amputation in OIP users (implant type not stated) as compared with socket prostheses users. A control group of socket prosthesis users acted as one comparator. The second comparator consisted of the pre-operative scores of the group before and two years after OIP (Table A4, Appendix 3).

Guidelines

The guideline identified two non-randomized comparative studies in which OIP (type not described) was compared with socket prosthesis for transfermoral amputation, and three case series, two of which reported on finger/thumb OIP, and one reporting on transfermoral OIP (Table A5, Appendix 3).

Outcomes

Systematic Reviews

One SR[4] reported on quality of life, function, activity, participation level, sitting comfort, and working status. The second SR[1] reported on quality of life, prosthetic use, mobility, problems, and global health, complications and adverse effects, patient satisfaction, gait analysis, radiographic evaluation, oxygen consumption, and costs associated with the prosthesis, services, repairs, and adjustments. Both SRs reported on condition-specific quality of life for studies using the “Questionnaire for Persons with a Transfemoral Amputation” (Q-TFA) scores, which measure four domains, including Prosthetic Use, Prosthetic Mobility, Problems, and Global Health. General quality of life was reported in both SRs from the Short Form (36) Health Survey (SF-36) scores, which measure eight subscales of mental and physical health, and one study included in one SR[4] utilized the revised short-form health survey (SF-6D), which assesses six dimensions. Follow-up ranged from one year to 10 years[4] and from three months to 17.5 years (Table A2, Appendix 3).[1]

Individual Clinical Studies

Quality of life as measured by the Q-TFA and SF-36, and functional outcomes, as measured by the Six Minute Walk Test (6MWT) and Timed Up and Go (TUG), were reported for two studies.[6,13] One study[13] also reported Amputation Mobility Predictor (AMPRO) scores. All three studies reported adverse events, including infection (graded according to severity), soft tissue refashioning surgery, revision surgery, fracture, and implant failure. One study[7] also reported hypergranulation, implant stability, osseous in-growth, stress shielding, and loosening. Follow-up for these three studies ranged from 10 months to 71 months, with a mean follow-up of 14 months,[6] 21.5 months,[13] and a median follow-up of 34 months.[7] One study[17] investigated detection thresholds of vibrometric stimuli at six frequencies (8, 16, 32, 64, 125, and 250 Hz) (Table A4, Appendix 3).

Guidelines

A comprehensive review process resulted in the development of an evidence overview. The evidence was not formally appraised, using a rating tool, but validity and generalizability were considered and reported. Opinion from specialist advisors was incorporated, public comment was solicited, and recommendations were developed (Table A5, Appendix 3).

Recommendations were made regarding patient information and consent, audit, clinical governance, research, and patient selection by a specialized team (Table A5, Appendix 3).

Summary of Critical Appraisal

A detailed summary of strengths and limitations of SRs, clinical studies, and the guideline is provided in Appendix 4.

Systematic Reviews

One of the SRs[1] mentioned a research protocol, but it was not provided. The other SR[4] did not report an a priori design, but did state that the PRISMA statement guidelines were followed. Both SRs provided research questions and inclusion and exclusion criteria. One SR[4] had two investigators to perform study selection with a process in place to resolve disagreements, but only had one investigator perform data extraction (another investigator reviewed the extracted data), while the other SR[1] reported neither duplicate study selection nor data extraction. In both SRs, a comprehensive literature search was performed in specified databases, with search terms provided, and the investigators also checked the references of all included articles for potentially missed studies. One SR[1] provided the years of the databases used and the date range of the search strategy, but the other SR[4] provided only the final search date. A search for grey literature was not mentioned in either SR. There were restrictions made on search and selection based on language in one SR[4] (English, Dutch, and German), and one SR[4] stated that they excluded conference abstracts. In both SRs, the authors did not state whether they searched for reports regardless of publication type or status. Neither SR included a list of excluded studies, but a table of included studies was provided for both. Detailed study characteristics were provided in both SRs. The scientific quality of the included studies was assessed and documented in both SRs, but in only one SR[4] was the scientific quality of the included studies used appropriately in formulating conclusions. In the other SR,[1] the limitations and inconsistencies that were identified for each study using GRADE were not formally rated, and did not seem to impact the stated conclusions. The decision to not pool the data for both SRs was appropriate given the significant heterogeneity in study design, outcomes and outcome measures, and follow-up periods. However, only one SR explicitly stated that meta-analysis was not possible due to heterogeneity.[4] One SR[1] included case series and presented noncomparative data mixed with comparative data, as well as overlapping study populations across the included studies. The same SR included at least one study reporting data on both upper and lower extremity amputation populations. Publication bias was not assessed or analyzed for one SR,[4] but it is mentioned in the other SR, though it was not formally analyzed.[1] Both SRs included a conflict of interest statement, but did not mention conflict of interest in the included studies (Table A6, Appendix 4).

Individual Clinical Studies

All three of the included studies that evaluated quality of life, function, and adverse events after OIP were similar in terms of strengths and limitations.[6,7,13] The objective of the studies was clearly described, main outcomes were described in advance with no unplanned subgroup analysis, and characteristics of patients were clearly described, as was the intervention. The main study findings were clearly described, with adverse events reported and standard deviation and/or confidence intervals reported. No patients were lost to follow-up. Because all of the studies were of a before-after design in the same participants, confounding was not an issue, nor was recruitment time period or compliance. However, other issues could influence the reported outcomes, including the duration of use of a prosthesis pre-operatively, the length of the residual limb, and the prosthetic components (e.g., knees, feet) used following OIP.[13] The statistical tests used to assess the main outcomes seemed to be appropriate. The main outcome measures used seemed valid and reliable; however, the grading scale used to rate infection level was developed by the authors in one study[13], and not reported in the other two,[6,7] Actual probability values were reported for only one study.[13] Power calculations were not provided for any of the three included studies. For all three studies the participants were not representative of all lower limb amputees, impacting generalizability. The selected participants had to demonstrate trouble with socket prosthesis use, and amputation had to be due to non-dysvascular causes. Participants with diabetes and peripheral vascular disease were excluded, as were people with psychological instability or mental illness. The staff, places and facilities where the patients were not described in two of the studies, and described as a specialized orthopedic osseointegrated clinic in the other.[7] In one study[13] prospective participants were screened online, while the other study employed a screening interview.[7] Recruitment details were not provided for the remaining study[6] (Table A7, Appendix 4). Due to the nature of the intervention and the tendency to use OIP only for patients with existing socket prosthesis issues, it was not feasible to randomize, conceal intervention assignment, or blind study participants or outcome evaluators. There did not appear to be an adjustment made for different lengths of follow-up in any of the included studies (Table A7, Appendix 4).

In the single study[17] performing vibrotactile evaluation in patients with either an OIP or a socket prosthesis, the objective and patient characteristics were clearly described. The main outcome to be measured was clearly described in the methods section, and the main findings were clearly described with estimates of random variability. The intervention was clearly described, although no details were provided on the type of prosthesis used in the OIP group. The distribution of confounders between the two study groups was clearly described, and an assessment of the impact of confounding variables was considered. Potential confounders were sex, and types of prosthetic equipment used across both groups. There was no loss to follow-up, and actual probability values were reported. It is not known whether the participants in the study were representative of the entire population from which they were recruited. However, participants with amputations caused by diabetes or arteriosclerosis, were excluded, impacting generalizability. It is not possible to determine whether the subjects who were prepared to participate were representative of the population from which they were recruited. It is not possible to determine whether the staff, places and facilities where the patients were treated are representative of the treatment the majority of patients receive. No blinding of either study participants or those measuring outcomes was reported, and randomization did not occur. No unplanned subgroup analyses were performed. Follow-up was equal for all participants. The statistical tests used to assess the main outcome appeared to be appropriate. Compliance was reliable. The patients in the different groups were not recruited from the same population, and were not recruited over the same period of time. A power calculation was not provided.

Guidelines

The overall objective, health questions covered, and population covered by the one guideline identified, was specifically described.[9,18] The views and preferences of the target population (patients, public, etc.) was sought via a public comment period, and the target users of the guideline were clearly defined. Systematic methods were used to search for evidence, and the methods for formulating the recommendations were clearly described at the guideline issuing body website. The criteria for selecting the evidence were not clearly described, and the strengths and limitations of the body of evidence were not clearly described, although some limitations were briefly discussed. The health benefits, side effects, and risks were considered in formulating the recommendations, and there was an explicit link between the recommendations and the supporting evidence. The guideline was externally reviewed by experts prior to its publication, and the recommendations provided are specific and unambiguous. The different options for management of the condition or health issue were clearly presented, and key recommendations were clearly identifiable. The guideline provided advice and/or tools on how the recommendations can be put into practice, and the potential resource implications of applying the recommendations were considered. However, the guideline did not describe facilitators and barriers to its application. The guideline presented monitoring and/or auditing criteria. It was not clear whether the guideline development group included individuals from all relevant professional groups, and competing interests of guideline development group members were not recorded and addressed. No procedure for updating the guideline was provided, and no statement was made regarding the views of the funding body having not influenced the content of the guideline (Table A8, Appendix 4).

Summary of Findings

A detailed summary of study findings of SRs and economic evaluations, as well as guideline recommendations is presented in Appendix 5.

What is the clinical effectiveness of osseointegrated prosthetic (OIP) implants for patients with lower limb amputation?

Quality of Life

One SR[4] reported that condition-specific quality of life as measured by the Q-TFA improved significantly after OIP as compared with socket prosthesis users, in the first and second years post-surgery. This outcome was based on five low-quality cohort studies. There was limited evidence from two low-quality cohort studies that general quality of life, as measured by the SF-36, improved significantly in the first and second years post-surgery for some sub-scales The other SR[1] did not provide any statistical analysis, but did provide comparative absolute scores for two of four studies that evaluated quality of life using the Q-TFA (two of the studies did not provide comparative data but only absolute scores), and reported increases for the OIP versus the socket prosthesis scores. The same SR reported an increase in comparative absolute SF-36 score values after OIP as compared with socket prosthesis use in one included study (Table A9, Appendix 5).

Two[6,13] of the four included clinical studies reported on quality of life as measured by the Q-TFA and the SF-36 in patients who received an OIP after experiencing socket-related difficulties. In both studies, quality of life was significantly improved after the OIP procedure as compared with the pre-operative values (Table A10, Appendix 5).

Function Level

One SR[4] reported on three low-quality cohort studies that assessed prosthesis wearing time using the Q-TFA prosthesis use score, and found that wearing time improved significantly with the use of the OIP relative to a socket prosthesis in the first and second years post-surgery. One study (included in both SRs) reported an average daily prosthetic use of 14 hours for OIP users compared with eight hours for socket prosthesis users.[1] Other low-quality studies reported that OIP users had a significantly larger range of hip motion, a gait more similar to that of healthy subjects, and improved kinematics as compared with socket prosthesis users (Table A9, Appendix 5).[4]

One SR[1] reported on one study evaluating walking ability with the 6MWT and the TUG test. The 6MWT results demonstrated that participants with an OIP walked significantly farther (27%) than those with a socket prosthesis. TUG test results demonstrated that participants with an OIP were significantly faster (44%) than those with a socket prosthesis (Table A9, Appendix 5).

Two[6,13] of the three included clinical studies reported significant improvements in both the Q-TFA global score, and the SF-36 physical component summary in OIP users as compared with pre-operative values. One of the studies[6] reported that all 10 patients who were wheelchair-bound before OIP were all walking at one-year follow-up, and another study[7] reported that all 21 patients who were wheelchair-bound pre-OIP were community ambulators after surgery. Similarly, another study[13] reported that all 14 patients who were wheelchair bound before OIP were walking post-operatively, with scores comparable to patients who were walking post-operatively (Table A10, Appendix 5).

One study[13] reported significant improvements in AMPRO scores, a measure of ability or potential to ambulate, with 30 out of 50 patients demonstrating improvement, and 20 patients remaining unchanged (Table A10, Appendix 5).

Activity Level

One SR[4] reported evidence from three low-quality cohort studies indicating that OIP users reported significant improvements in overall mobility, capability, and walking habit scores as compared with socket prosthesis users, based on their responses to the Q-TFA, in the first and second years post-surgery. Evidence from other low-quality studies demonstrated improvements in sitting comfort and walking ability, as well as reductions in the energy cost of walking in OIP users as compared with socket prosthesis users (Table A9, Appendix 5).[4]

Participation Level

One SR[4] reported evidence from one low-quality cohort study that showed no differences in 'work situation' two years after OIP (Table A9, Appendix 5).

Adverse Events

One SR[1] reported the complication rates after OIP as reported for all included studies as follows: skin complications (n = 3 studies, range 30% to 54%); skin colonization (n = 2 studies, range 4% to 44%), skin infection (n = 4 studies, range 28% to 55%); implant infection (n = 7 studies, range 2% to 41%); early infection (n = 1 study, 16%); late infection (n = 1 study, 25%); implant loosening (n = 4 studies, range 2% to 6%); peri-prosthetic fracture (n = 3 studies, range 0% to 9%); revision surgery (any re-operation, n = 7 studies, range 8 % to 67%); and explant (n = 9 studies, range 3% to 18%, Table A9, Appendix 5).

Three of the included clinical studies reported adverse events.[6,7,13] One study followed 23 patients for a mean of 14 months, and reported 15 cases of minor infection in 12 patients (of which 12 case responded to oral antibiotics, while three cases responded to intravenous antibiotics).[6] Elective soft tissue refashioning was performed in six patients. There were no cases of revision surgery, fracture, or implant failure recorded (Table A10, Appendix 5).[6]

One of the included clinical studies[13] with a mean follow-up of 21.5 months reported a total of 27 adverse events in 50 patients (54%). Twenty-one patients experienced one or more infections, with 13 responding to oral antibiotics, five to intravenous antibiotics, and three requiring surgical debridement. Soft tissue refashioning was performed in 10 patients to avoid impingement, skin irritation, and infection. Four patients who were wheelchair-bound with severe osteoporosis before OIP experienced peri-prosthetic fractures that were managed without interfering with the osseointegration of the implant. Implant revision was required in two patients, one in whom osseointegration did not occur due to an undersized device, and one due to implant failure fatigue at 3.5 years (Table A10, Appendix 5).[13]

One prospective cohort study[7] reported on the safety of OIP in 86 patients with 91 implants, with a median follow-up of 34 months (range 24 months to 71 months). Adverse events were reported in 55 (64%) patients, while 31 patients (36%, 32 implants) had an uneventful course. Twenty-nine patients (34%, 31 implants) had one or more infections, for a total of 47 infections. Of the reported infections, 23 patients (27%, 41 infections) responded to oral antibiotics one responded to parenteral antibiotics, and one required treatment with local debridement. Four patients had a high-grade soft-tissue infection treated with surgical debridement. No cases of bone infection or septic implant failure were reported. Hypergranulation of the stoma was reported in 17 patients (20%) on 22 occasions, treated with chemical cauterization, and excision of the redundant soft tissue was required in 14 patients (16%) on 23 occasions. Three patients (3%) fell and sustained a traumatic fracture proximal to the OIP, but implant removal was not necessary. One patient had the implant replaced due to undersizing, and the implant was replaced in two patients due to breakage of the intramedullary component at 42 and 47 months after surgery. Twenty-five patients (29%, 30 events) had breakage of the pin used as a safety weak point[7] Radiographs demonstrated stable osseous growth and no implant migration, except in one patient. Rounding and resorption of the distal femoral cortex was seen in 20% of patients at one year follow-up, and in 10% of patients, hypertrophic bone formation was observed in the distal part of the femur (Table A10, Appendix 5).[7]

One prospective cohort study[7] evaluated risk factors for adverse events after OIP. They reported that smokers had a seven-fold higher risk of developing recurrent infection. The same study identified that women had a more than six-fold increase in the risk of developing a severe infection, and that a BMI of greater than 25 kg/m^2 was associated with a three-fold higher risk of mild infection (Table A10, Appendix 5).[7]

Patient Satisfaction

One SR[1] reported on two studies in which 37 out of 39 patients would choose an OIP again if given the choice, for a 95% satisfaction rate (Table A9, Appendix 5).

Prosthesis Migration and Rotation

One SR[1] included one study that evaluated proximal-distal migration of the OPRA prosthesis using radio stereometric analysis and found this to be 0.17mm on average. Rotation of the prosthesis was found to be on average 0.38 degrees. Follow-up ranged from six months to 10 years post-surgery (Table A9, Appendix 5).

Cortical Thinning and Cancellization

One SR[1] included one study with follow-up ranging from six months to 10 years post-surgery that reported cortical thinning and cancellization in all 55 patients and trabecular streaming in three, based on evaluation of plain radiographs, indicating stable fixation of the implant (Table A9, Appendix 5).

Oxygen Consumption

One SR[1] reported data from one study demonstrating that oxygen consumption was significantly less (18%) in OIP users than in socket prosthesis users during treadmill walking (Table A9, Appendix 5).

Vibration

One study[17] reported data on vibrotactile evaluation, and found that that study participants with an OIP had significantly improved ability to detect vibrations through the prosthesis at 125 Hz at two-year follow-up as compared with the preoperative socket prosthesis measurement. Also, compared with a control group of socket prosthesis users, the OIP participants had a significantly better ability to detect high frequency vibrations (125 Hz and 250 Hz) through the prosthesis. The authors suggested these findings could potentially lead to advantages in gait control for patients with an OI prosthesis (Table A10, Appendix 5).

What is the cost-effectiveness of osseointegrated prosthetic implants for patients with lower limb amputation?

One SR[1] provided cost data based on a single study published in 2013 comparing OIP with socket prosthesis users. The mean annual total costs of the new prosthesis, services, repairs and adjustments, were 14% lower for OIP than for socket prostheses (€ 3149 versus € 3672, respectively). While there were fewer office visits with OIP users (3.1 vs. 7.2 visits per year), material costs were higher for OIP, making the annual mean costs for osseointegrated and socket prostheses similar. This study did not evaluate the cost of the implant, surgeries, hospitalization, medical check-ups and the possible costs of dealing with complications (Table A9, Appendix 5).

What are the evidence-based guidelines regarding the use of osseointegrated prosthetic implants in patients with lower limb amputation?

One 2008 guideline[18] determined that OIP may have potential advantages for some patients as compared with socket prostheses. But due to a lack of evidence and long-term follow-up, they recommended that OIP should only be used with "...special arrangements for clinical governance, consent and audit or research."[18] The guideline recommended that patients be informed about the uncertainty around the safety and efficacy of osseointegration, particularly over the long term, and that they be provided with clear written information. It was recommended that clinicians performing OIP procedure audit and review the clinical outcomes of all patients using specified audit criteria and an audit tool, and that patient selection be carried out by a multidisciplinary team, composed of a surgeon experienced in amputation and in the necessary bone and soft tissue reconstruction, and rehabilitation specialists with expertise in prosthetics and implant design. Collaboration among clinicians in the collection and publication of data, particularly in relation to adverse events such as infection and long-term performance of the implants, was recommended (Table A11, Appendix 5).

Limitations

Generalizability

Socket-related problems are the main reason for patients to receive an OIP, and hence the socket prosthesis users that are used as comparators in the included studies may not be representative of the general population of socket prosthesis users.[4] Additionally, as previously stated, the most common cause of lower limb amputation in Canada is due to dysvascular causes, commonly as a result of diabetic complications[2,3] However, all of the studies included in this Rapid Response did not include amputees with dysvascular indications, and hence the results may not be generalizable to this population. Finally, all of the studies included in this Rapid Response report were conducted in other countries. This may or may not impact the generalizability of the findings to Canadian patients.

Heterogeneity

There was considerable heterogeneity across nearly all aspects of the included studies. There are significant differences in the included patient populations, implant materials and design, the OIP implant type and procedure, rehabilitation protocols, follow-up periods, outcome measures.

One of the included SRs[4] noted that that those experiencing socket related problems before OIP surgery had outcomes at baseline that were inferior to those of socket prosthesis users in general, which could over-estimate the impact of OIP.[4] Other factors, such as the duration of use of a prosthesis pre-operatively, the length of the residual limb, and the prosthetic components (e.g., knees, feet) used following OIP, could all impact the clinical improvements observed.[13] Only one of the included studies included details on the prosthetic components used during the study period.[17] Device design changes occurred within and among studies,[1] as well as protocols for soft-tissue management[7], both of which could impact observed outcomes. Finally, one SR included at least one study that included both upper and lower limb amputations,[1] and one study[7] included bilateral amputees.

Study Design

Socket prosthesis problems tend to be one of the primary eligibility criteria to receive an OIP. Hence, it is currently not possible to randomize patients to receive an OIP.[4] One of the included SRs[1] included predominantly noncomparative studies, which does not permit an evaluation of the OIP as compared with socket prosthesis use or no prosthesis use. While the limitations of the included studies in this SR[1] were detailed, no overall grade of evidence each study was provided. Among the limitations reported were retrospective study design, small sample sizes, failure to report outcomes, and loss to follow-up. The other SR included only two studies that reported comparative data for socket prosthesis users that was not taken from a before-after study design, and reported limitations including a lack of adjustment for confounding variables and failure to blind assessors and participants. With the exception of the study evaluating vibrotactile response, the individual clinical studies included in this Rapid Response report also were of a before-after design, and did not include a control group. Without a control group, it is possible that another factor may be influencing the observed outcomes.

Evaluation Methods

There is a lack of consensus about the instruments that should be used to evaluate interventions with a lower extremity amputation, which hinders comparison of studies and the generalizability of findings.[4] In one SR[4] there was overlap in only three instruments used across all seven included studies. The other included SR[1] reported a wide variety of outcomes measured and reported across studies, with only complications being reported for most included studies. Infection was classified by non-formal measures in the three included studies reporting adverse events.[6,7,13]

Overlapping Study Populations

There were strong indications that one of the included SRs[1] may have included studies with overlapping populations. Additionally, of the 4 included clinical studies, three were published by the same author, suggesting that there might be overlapping populations.[6,7,13] One of the included clinical studies[7] was a two-centre study, and reported data already published in a previous study from one of the centres (reported in both of the included SRs[1,4]).

Follow-up

Long-term follow-up is not available for some of the more recent devices in the included studies, which precludes assessment of the long-term risk of infection.[7] Because of the abutment protruding through the skin, deep infection could arise over time, leading to serious adverse events.[10] One SR[4] had follow-up of one to two years post-OIP in six of the seven included studies. The other SR[1] reported a wide range of follow-up (3 months to 17.5 years), though the follow-up mean and range was not included for some studies. For three of the included studies,[6,7,13] mean or median follow-up ranged from just 14 to 34 months. In general, long-term data from low-quality studies is available only for the OPRA implant.

Conclusions and Implications for Decision or Policy Making

The quality of evidence to support the use of OIP for lower limb loss is general low. Current practice patterns preclude study designs of higher methodological quality as socket prosthesis-related issues are generally considered a requirement for OIP.[4] While the tools used to rate study design would generally rate a longitudinal cohort study with before and after design as methodologically weak; however, it has been suggested that this type of study design is likely a good and ethical way of comparing osseointegrated and socket prostheses.[4] Despite the low quality of evidence, investigators consistently reported significant improvements in quality of life, function and mobility after the OIP procedure. Many patients who were wheelchair-bound pre-procedure were able to walk after OIP.[7,13] Further, it has been suggested that OIP enables amputees to attain function close to that of an able-bodied individual.[7] Patient satisfaction with an OIP has generally been rated as high.[1]

Adverse events associated with the OIP implant are a potential concern. In one study evaluating the safety of OIP using the ILP and OPL, 64% of patients experienced at least one complication.[7] A wide range of revision rates and explant rates were reported across the included clinical studies and SRs. Infection is quite common, particularly around the transcutaneous connection, and occurred in almost half of all patients in one SR.[1] Implant infection rate varied from 2% to 41%.[1] In the studies included in the Rapid Response, it does not appear that a formal test is used to grade infections, and in some studies, the follow-up period is not long enough to identify potential cases of infection.[13] Without a biological barrier, deep infection, osteomyelitis, and prosthesis removal are potentially likely over time.[10]

The design of and materials used for the prosthetic implant are another important consideration thought to affect efficacy and adverse events.[6] Device design changes occurred within and among many of the EEFP studies included in one SR, with resulting decreases in skin complication rates.[1] One study evaluated the EEFP-ILP across three different iterations and after a follow-up period ranging from one month to 144 months (after date of implant), the authors reported a significant reduction in infection rates with the newer designs[11] Another study modified soft tissue handling methods during the study period to reduce skin irritation and infection.[7] Peri-implant soft tissue protocols are considered essential to reduce adverse events, particularly infection.[7] One author stressed the learning curve associated with implementation of a new intervention.[7] Comparisons across the different types of OIPs were not identified.

It is thought that different protocols can significantly affect the time from surgery to unaided walking after OIP.[13] The Osseointegration Group of Australia Accelerated Protcol-1 (OGAAP-1) is a program that aims to reduce the time required for reconstruction and rehabilitation.[13] The protocol emphasizes an integrated approach including initial patient screening, pre-operative care, the surgical procedure, rehabilitation, and ongoing post-operative care.[13] The time from surgery to unaided walking using this protocol was 4.5 months in one study, versus the nine to 12 months reported in other studies[13] Comparisons across the different types of rehabilitation protocols were not reported in the included studies.

Patient selection is a potentially important consideration. The OIP procedure is currently an option when the cause of amputation is trauma, cancer, or when a socket prosthesis user is experiencing problems.[4] The literature generally agrees that, due to infection risks, OIP is not indicated for amputations resulting from vascular causes.[4] One of the included SRs reported inclusion of six to 11% of participants whose amputation was due to causes other than trauma and cancer, e.g., arterial embolus and infection, suggesting that eligibility criteria for an OIP could be broadened; however no data was presented for this group specifically to support this statement, and the authors caution that more research is needed.[4] Patients who smoke are sometimes excluded from OIP trials,[6,13] and one study[7] reported that smokers had a seven-fold higher risk of developing recurrent infection. The same study identified that women had a more than six-fold increase in the risk of developing a severe infection (but not other levels of infection), and that a BMI of greater than 25 kg/m^2 was associated with a three-fold higher risk of mild infection.[7] Disuse osteoporosis is common in those that are wheelchair bound or that use a socket prosthesis. When these patients are fitted with an OIP, the resulting increase in activity and potential for trauma can lead to fractures, suggesting that screening, monitoring bone mineral density, and active treatment of osteoporosis may have a potential role.[7] These results indicate that careful patient selection and counselling may be useful criteria to optimize successful OIP.[7] The included guideline[18] recommended that patient selection for OIP be carried out by a multidisciplinary team, composed of a surgeon experienced in amputation and in the necessary bone and soft tissue reconstruction, and rehabilitation specialists with expertise in prosthetics and implant design.

Only one study (2013) determined that the overall costs for both OIP and socket prostheses were similar given the total costs for the new prosthesis, services, repairs, and adjustments, when factoring in fewer office visits for OIP users.[1] However, it is important to note that this evaluation did not incorporate procedural and hospital costs, or adverse events and associated costs.

References

1. van Eck CF, McGough RL. Clinical outcome of osseointegrated prostheses for lower extremity amputations: a systematic review of the literature. Current Orthopaedic Practice. 2015;26(4):349-57.

2. Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R. Estimating the prevalence of limb loss in the United States: 2005 to 2050. Arch Phys Med Rehabil. 2008 Mar;89(3):422-9.

3. Kayssi A, de Mestral C, Forbes TL, Roche-Nagle G. A Canadian population-based description of the indications for lower-extremity amputations and outcomes. Can J Surg [Internet]. 2016 Apr [cited 2017 Feb 1];59(2):99-106. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4814278

4. Leijendekkers RA, van Hinte G, Frolke JP, van de Meent H, Nijhuis-van der Sanden MW, Staal JB. Comparison of bone-anchored prostheses and socket prostheses for patients with a lower extremity amputation: a systematic review. Disabil Rehabil. 2016 Aug 5;1-14.

5. Rapid review of osseointegration/ direct skeletal fixation: a report for NHS England. London (England): Bazian Ltd.; 2016 Mar.

6. Al Muderis M, Lu W, Li JJ. Osseointegrated Prosthetic Limb for the treatment of lower limb amputations : Experience and outcomes. Unfallchirurg. 2017 Jan 9. Epub ahead of print.

7. Al Muderis M, Khemka A, Lord SJ, van de Meent H, Frolke JP. Safety of osseointegrated implants for transfemoral amputees: a two-center prospective cohort study. J Bone Joint Surg Am. 2016 Jun 1;98(11):900-9.

8. Lewis J, Pierce G, Russo S, Kuzminski K, Wagner B. The impact of osseointegrated prosthesis on quality of life in patients with tansfemoral amputation: a systematic review [Internet]. Scranton (PA): University of Scranton; 2016. [cited 2017 Feb 17]. Available from: http://www.scranton.edu/academics/pcps/physicaltherapy/images/research-night-ppts/group7-lewis-pierce-russo-kuzminski.pdf

9. Interventional procedure overview of direct skeletal fixation of limb or digit prostheses using an intraosseous transcutaneous implant [Internet]. London (England): National Institute for Health and Clinical Excellence (NICE); 2008 Jan. [cited 2017 Feb 1]. (Interventional procedures programme). Available from: https://www.nice.org.uk/guidance/ipg270/resources/direct-skeletal-fixation-of-limb-or-digit-prostheses-using-intraosseous-transcutaneous-implants-interventional-procedures-overview2

10. Dougherty PJ, Smith DG. One step forward, but a need for caution: commentary on an article by Munjed Al Muderis, et al.: "Safety of osseointegrated implants for transfemoral amputees. a two-center prospective cohort study". J Bone Joint Surg Am. 2016 Jun 1;98(11):e48.

11. Juhnke DL, Beck JP, Jeyapalina S, Aschoff HH. Fifteen years of experience with Integral-Leg-Prosthesis: cohort study of artificial limb attachment system. J Rehabil Res Dev. 2015;52(4):407-20.

12. Haket LM, Frolke JP, Verdonschot N, Tomaszewski PK, van de MH. Periprosthetic cortical bone remodeling in patients with an osseointegrated leg prosthesis. J Orthop Res. 2016 Jul 28.

13. Al Muderis M, Tetsworth K, Khemka A, Wilmot S, Bosley B, Lord SJ, et al. The Osseointegration Group of Australia Accelerated Protocol (OGAAP-1) for two-stage osseointegrated reconstruction of amputated limbs. Bone Joint J. 2016 Jul;98-B(7):952-60.

14. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2017 Feb 27];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

15. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2017 Feb 27];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

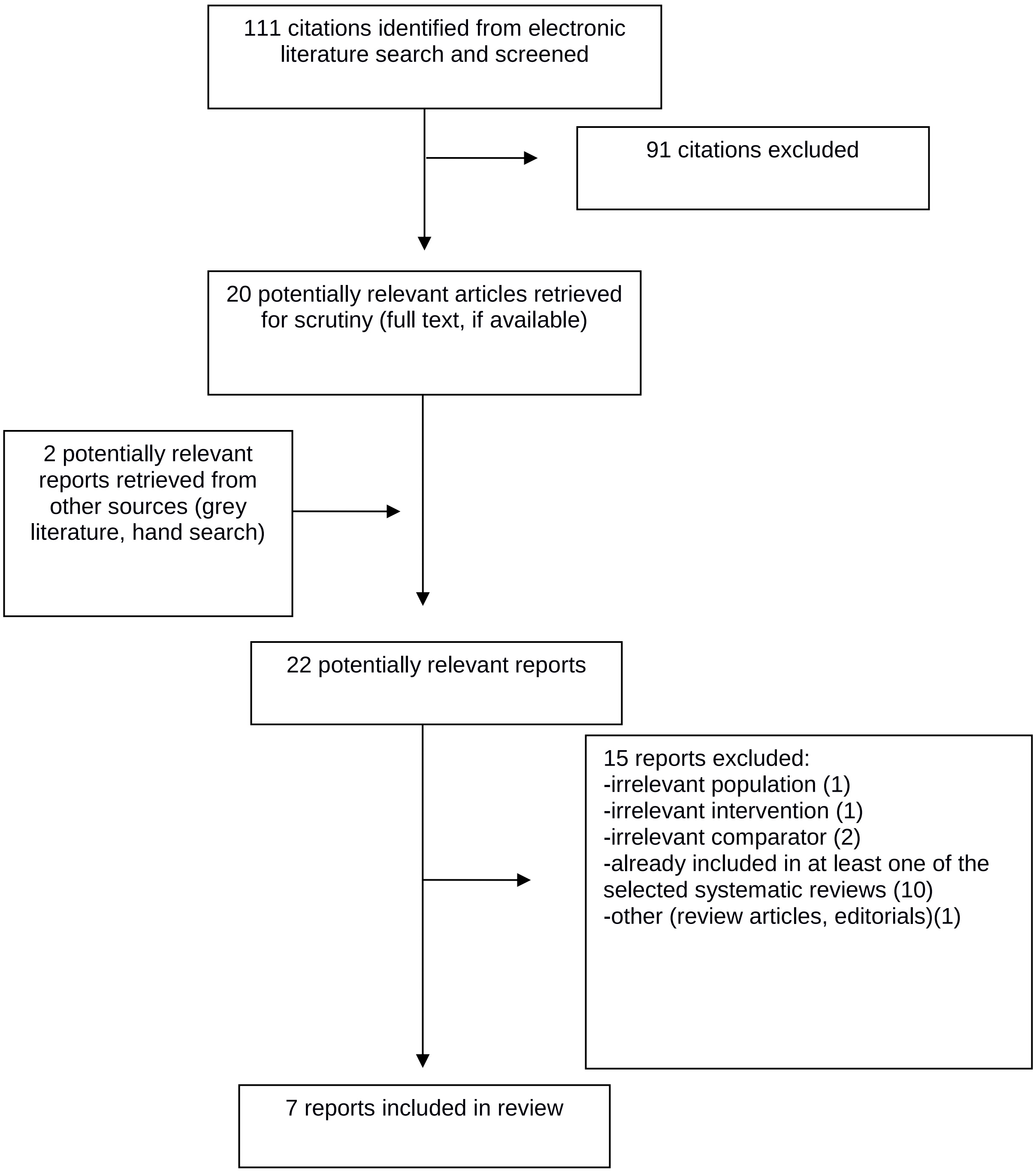
16. Brouwers M, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in healthcare. CMAJ [Internet]. 2010 Dec [cited 2017 Feb 27];182(18):E839-E842. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3001530/pdf/182e839.pdf

17. Haggstrom E, Hagberg K, Rydevik B, Branemark R. Vibrotactile evaluation: osseointegrated versus socket-suspended transfemoral prostheses. J Rehabil Res Dev. 2013;50(10):1423-34.

18. Direct skeletal fixation of limb or digit prostheses using intraosseous transcutaneous implants. Interventional procedures guidance [Internet]. London (England): National Institute for Health and Care Excellence; 2008 Jul 23. [cited 2017 Jan 30]. Available from: https://www.nice.org.uk/guidance/ipg270/resources/direct-skeletal-fixation-of-limb-or-digit-prostheses-using-intraosseous-transcutaneous-implants-1899865571125957

19. Frölke JP, Leijendekkers RA, van de Meent H. Osseointegrated prosthesis for patients with an amputation : Multidisciplinary team approach in the Netherlands. Unfallchirurg. 2017 Jan 17. Epub ahead of print.

Appendix 1: Selection of Included Studies



Appendix 2: Osseointegrated Prostheses and Procedures

Table A1: Summary of Osseointegrated Prostheses Implants and Procedures

Prosthesis/Company/ Year of Introduction/Development	Implant and Technique Details	Countries Offering Technique
Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA) Integrum, Molndal, Sweden 1990	<u>Implant</u> Titanium screw- fixation, with a length of 80 mm[4,19] <u>Procedure</u> • Second procedure after 6 months[4,5] • Involves splitting muscles at the end of the implant and suturing them to the bone, leaving a portion of 5mm bare bone covered by skin that has had the subcutaneous fat removed[5] <u>Skin Integration</u> Skin is attached to the bone by a grafting after the intraosseous device has integrated[1] <u>Rehabilitation</u> • Normal speed 6 months (or half speed 12 months)[5] • Immobilisation for 1-2 weeks[5] • Training with short prosthesis starting with 20kg at 4-6 weeks[5] • Training with full prosthesis 11-13 weeks[5] • Discuss when can walk without a walking aid at 24 weeks[5]	Sweden, Australia, Belgium, Denmark, France, The Netherlands, Portugal, Spain, Australia, USA and Chile[5]
Endo-Exo Femur Prosthesis (EEFP), now termed Integral-Leg-Prosthesis (ILP) Sana Clinics, Lübeck, Germany 1999	<u>Implant</u> • A press-fit, 140 to 180 mm-long, slightly curved chromium–cobalt–molybdenum or titanium stem with a macroporous or roughly coated surface, press-fit[19] • 3 different iterations since 1999 described in detail elsewhere[11] <u>Procedure</u> • 2nd operation after 6 weeks[4,5] <u>Skin Integration</u> • The skin is not attached to the deeper structures[1] <u>Rehabilitation</u> • Partial weight-bearing 5-10kg with crutches and vertical posture immediately after second surgery[5] • Full weight-bearing without crutches after 4 to 6 weeks[5]	Germany, The Netherlands, Australia[5]
Intraosseous Transcutaneous Amputation Prosthesis (ITAP) Stanmore Implants Ltd, UK Year not reported	<u>Implant</u> • Material unknown, the flange is macrotextured and coated with hydroxyapatite[1] <u>Procedure</u> • 1 single operation[1] <u>Skin Integration</u> • Keratinocytes must attach to the implant surface to avoid infection caused by breaching of the skin at the implant interface[1] <u>Rehabilitation</u> • Details unknown	Only available as part of a pre-CE mark (i.e., exclusively for clinical investigations) clinical study in the United Kingdom[5]

Prosthesis/Company/ Year of Introduction/Development	Implant and Technique Details	Countries Offering Technique
Osseointegration Prosthetic Limb (OPL) now termed Osseointegration Group of Australia Osseointegration Prosthetic Limb (OGAP-OPL) 2011[5] to 2013[6]	<u>Implant</u> Titamium alloy, press-fit[6] <u>Procedure</u> • 1 single operation or 2nd operation after 6 to 8 weeks[5] • Redundant skin and any bone spurs are removed, muscle groups are rearranged and soft tissue fat is removed[5] <u>Rehabilitation</u> • Partial weight-bearing and fitting of prosthesis days after surgery[5]	Australia[5]

Appendix 3: Characteristics of Included Publications

Table A2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Types and numbers, and dates of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Leijendekkers, 2016, The Netherlands[4]	N = 7 studies (n = 5 before and after cohort studies published between 2008 to 2014; n = 2 cross-sectional studies published in 2005, 2010.	Cohort Studies N = 110 participants with a transfemoral amputation, sample size: 18 to 51: Age: 20 to 70 years; higher ratio of females to males in 3 studies; Time from primary amputation: 10 months to 45 years. Primary reason for amputation: trauma, with some tumour and 'other' indications, including arterial embolus and infection. Cross-Sectional N = 32 bone-anchored prosthesis users with a transfemoral amputation, sample size 12 to 20 participants; age: 26 – 67 years; higher ratio of males to females in both studies; time from primary amputation: 6 – 46 years. Primary reason for amputation : trauma, with some tumour and 'other' indications.	OPRA, n = 6 studies (two-step surgery and rehabilitation); Sweden EEFP, n = 1 study (two-step surgery and rehabilitation); The Netherlands	Cohort Studies N = 7 studies, Socket prosthesis N = 1 study, fifty-seven; age-, side- and gender-matched healthy control subjects Cross-Sectional N= 185 socket prosthesis users with a transfemoral amputation, sample size: 43 to 142 participants; age: 28 to 70 years; Time from primary amputation: 2 to 56 years.	Sitting comfort, working status, QoL, function, activity, participation level Follow-up: 2 years after step 2 (n = 3 studies); at least 1 year after step 2 (n = 3 studies); median 5 years (range 2 to 10) after step 2 (n = 1 study).
Van Eck, 2015 [1], US	N = 13 studies (n = 7 retrospective cohort, published between 2003 to	N = 540, with sample size ranging from 11 to 100; Higher ratio of	OPRA, n = 7 studies, 2-step, 6 in Sweden, 1 in United Kingdom Sweden,	Not stated but socket prosthesis assumed (many before and after	QoL as measured by the SF-36 and prosthetic use, mobility, problems,

First Author, Publication Year, Country	Types and numbers, and dates of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
	2012, n = 3 prospective cohort published between 2008 to 2014, n = 3 retrospective comparative published between 2005 to 2013	males to females in n = 9 studies, NR in 3 studies; Age: 17 to 78 years; n = 2 study included upper and lower extremity amputations. Amputation location not explicitly stated for all studies but lower extremity amputation assumed due to inclusion criteria; Primary reason for amputation: trauma, with some tumour and 'other' indications.	Norway and Spain EEFP, n = 5 studies, 2-step, 1 in The Netherlands, 4 in Germany ITAP, n = 1 study, 1-step, United Kingdom	studies included)	and global health as measured by the Q-TFA; Complications and adverse effects; Patient satisfaction, gait analysis, radiographic evaluation, oxygen consumption, and health care costs. Follow-up, 3 months to 17.5 years

EEFP = Endo–Exo Femoral Prosthesis; ITAP = Intraosseous Transcutaneous Amputation Prosthesis; OPRA = Osseointegrated Prostheses for the Rehabilitation of Amputees; Q-TFA = Questionnaire for Persons with a Transfemoral Amputation; QoL = Quality of Life; SF-36 = Short Form (36) Health Survey.

Table A3: Overlap Between Included Systematic Reviews

Primary Study Author, Publication Year	Systematic Review Author, Publication Year	
	Leijendekkers, 2015[4]	Van Eck, 2015[1]
Aschoff, 2009		*
Aschoff, 2010		*
Aschoff, 2011		*
Aschoff, 2012		*
Branemark, 2014	*	*
Frossard, 2010	*	
Hagberg, 2005	*	*
Hagberg, 2008	*	*
Hagberg, 2009		*
Hagberg, 2013		*
Hagberg, 2014	*	
Nebergall, 2012		*
Sullivan, 2003		*
Tillander, 2010		*
Tranberg, 2011	*	
Van de Meent, 2013	*	*

Table A4: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Muderis, 2017[6] Australia	Retrospective data analysis (before-after)	N = 23 unilateral transfemoral amputees, experiencing difficulty using a socket prosthesis (n = 17 men, n = 6 women) Age: 20 – 67 years (average 46.2 years) Cause of	OPL Implant No interval between stages reported (single operation possible)	Socket prosthesis (n = 12); No prosthesis (n = 10 patients, wheelchair bound)	QoL: Q-TFA, SF-36 Functional: 6MWT, TUG Adverse events: Infection (graded into four levels from 1 (low grade = soft tissue) to 4 (high = septic implant failure);

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
		amputation: trauma (n = 16); neoplasia (n = 4; infection (n = 2) Implant date: Between December 2013 and November 2014			refashioning surgery (elective soft tissue); revision surgery; fracture; implant failure Mean follow-up = 14 months (range 10 – 30 months)
Muderis, 2016[13] Australia	Prospective before-after cohort	N = 50 unilateral transfemoral amputees with socket or prosthesis fitting problems (n = 34 men, n = 16 women) Age: 24 to 73 years, mean = 48.4 years Cause of amputation: Trauma, n = 32; blast injury, n = 3, infection, n = 5, oncology, n = 8, congenital, n = 2 Time from amputation to OIP surgery: range from < 2 years to 65 years Implant date: March 2011 to June 2014	ILP or OLP (numbers not reported) Two surgical stages 4 – 8 weeks apart; both implanted under the OGAAP-1 protocol	Socket prosthesis, n = 36 No prosthesis, n = 14 patients, wheelchair bound	Q-TFA, SF-36, TUG, 6MWT, AMPRO Radiological assessment (CT) and BMD measurement Adverse events: soft tissues problems, infection (graded using a 5-level system from 0 = no infection to 4 = implant failure), fractures, implant failure Mean follow-up = 21.5 months after the first stage; Routine follow-up at six weeks, and 3, 6, and12 months post-operatively

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Muderis, 2016[7] Australia The Netherlands	Prospective before-after cohort (two-centre)	N = 86 patients (n = 91 implants; n = 65 men, n = 21 women); n = 65 experiencing socket-related issues, n=21 wheelchair-bound; Age: 25 to 81 years n = 6 smokers BMI: <25 kg/m^{2}: 33 >25 kg/m^{2}: 53 Bilateral amputation: n = 5 Cause of amputation: trauma, n = 65 tumour, n = 11 infection, n = 8, congenital, n = 1 other, n = 1 Prosthesis users for between zero to 63 years before OIP Implant date: 2009 to 2013	ILP Two-stage surgical procedure with 6 – 8 weeks between stages Rehabilitation with either the OGAAP at the Australian centre, or other protocol in The Netherlands		Walking ability, infection graded from 1 (low-grade soft tissue infection) to 4 (septic implant failure), hypergranulation, implant stability, osseous in-growth, stress shielding, loosening, implant francture Median follow-up = 34 months (range 24 to 71 months) Radiographs at 3 months and 6 months, at one year, and then annually.

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Haggstrom, 2013[17] Sweden	Non-randomized controlled study (before-after, and a control group)	OIP Group N = 17 patients (n = 8 males, n = 9 females); unilateral transfemoral amputation, socket prosthesis users Mean age 44.6 years (range: 23 to 63 years) Mean time since amputation 14.5 years (range: 2 to 42 years) Cause of amputation: n = 11 trauma, n = 6 tumour Implant date: 1998 to 2007 Control group N = 17 (11 males and 6 females; unilateral transfemoral amputation; socket prosthesis users Mean age 43.2 years (range: 29 to 63 years) Mean time since amputation 18 years (range: 2 to 34 years) Cause of amputation: trauma, n = 11 trauma; tumour, n = 6	Vibrometric evaluation on the prosthetic and intact feet were conducted at six frequencies (8, 16, 32, 64, 125, and 250 Hz)	N = 17 socket suspended prosthesis (before-after), on the socket prosthesis and then the OIP foot, and the intact foot. N = 17 socket prosthesis users, prosthetic and intact foot (control group)	Vibrometric evaluation (detection thresholds of vibrometric stimuli) 2-year follow-up (post-implant)

6MWT = Six Minute Walk Test; AMPRO = Amputation Mobility Predictor; BMD = bone mineral density; CT = computed tomography; ILP = Integral Leg Prosthesis; OGAAP-1 = Osseointegration Group of Australia Accelerated Protocol; OPL = Osseointegrated Prosthetic Limb; Q-TFA = Questionnaire for Persons with a Transfemoral Amputation; QoL = Quality of Life; SF-36 = Short Form (36) Health Survey; TUG = Timed Up and Go

Table A5: Characteristics of Included Guidelines

Intended Users; Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Evidence Quality and Strength	Recommendation Development and Evaluation	Guideline Validation
Clinicians People with a limb or digit amputation	Direct skeletal fixation of limb or digit prostheses using OIP	Efficacy and adverse events of OIP	A rapid review of the medical literature and specialist opinion.	No formal evaluation of evidence is used. Validity and generalizability considered.	A rapid review of the medical literature and specialist opinion from 3 advisors	4-week consultation

OIP = osseointegrated prosthesis

Appendix 4: Critical Appraisal of Included Publications

Table A6: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR14

Strengths	Limitations
Leijendekkers[4]	
A research question and inclusion/exclusion criteria were provided, though it was not clear if they were developed a priori (the authors stated that the PRISMA statement guidelines were followed).	Just one investigator extracted data (results were checked by another investigator).
Two investigators independently selected studies with disagreements resolved by discussion	It was not clear what the start date of the literature search was, nor were the years of the databases used reported in the main paper.
A comprehensive literature search was performed in 5 specified databases, with search terms (keywords and MESH) provided. Search strategy is available in supplementary material. The investigators also checked the references of all included articles potentially missed studies.	No statement was made regarding a search for grey literature.
A list of included studies was provided.	A list of excluded studies was not provided.
Detailed characteristics of the included studies were provided.	There was no statement or assessment regarding likelihood of publication bias.
The scientific quality of the included studies was assessed and documented.	Conflict of interest was not assessed in the included studies.
The scientific quality of the included studies was used appropriately in formulating conclusions.	The authors did not state whether they searched for reports regardless of publication type, but did state that they excluded conference abstracts.
The methods used to combine the findings of studies appropriate given the significant heterogeneity.	
A conflict of interest statement was included for the SR authors.	
Van Eck[1]	
A research question and inclusion/exclusion criteria were provided; a research protocol was developed a priori, but not provided.	There was no statement regarding duplicate study selection or data extraction.
A comprehensive literature search was performed in 3 specified databases, with search terms (keywords and MESH) provided. The investigators also checked the references of all included articles for potentially missed studies. The years of the databases used were included and the years of the search strategy were provided. Keywords were provided.	No statement was made regarding a search for grey literature.
A list of included studies was provided.	A list of excluded studies was not provided.
Detailed characteristics of the included studies were provided.	Publication bias was mentioned but not analyzed or assessed.
The scientific quality of the included studies was assessed and documented.	The methods used to combine the findings of studies were not particularly useful given that absolute values were reported for non-comparative studies, and statistical analysis was not

Strengths	Limitations
	provided.
A conflict of interest statement was included for the SR authors.	The scientific quality of the included studies was not used appropriately in formulating conclusions, as the limitations and inconsistency issues were not mentioned in the conclusion
	The authors did not state whether they searched for reports regardless of publication type.
	Conflict of interest was not assessed in the included studies.

Table A7: Strengths and Limitations of Included Studies using the Downs and Black Checklist[15]

Strengths	Limitations
Muderis, 2017[6]	
The objective of the study was clearly described.	Actual probability values were not reported.
The main outcomes were clearly described in the methods section.	It is not known whether the participants in the study were representative of the entire population from which they were recruited. The study inclusion criteria require participants to experience socket prosthesis issues, which impacts generalizability and could potentially overestimate the effect of the intervention. Patients with diabetes, vascular disease, and psychological instability were excluded, impacting generalizability.
The characteristics of the included patients were clearly described, and detailed inclusion and exclusion criteria were reported.	It is not possible to determine whether the subjects who were prepared to participate were representative of the population from which they were recruited.
The intervention of interest was clearly described.	It is not possible to determine whether the staff, places and facilities where the patients were treated are representative of the treatment the majority of patients receive.
The main study findings were clearly described.	It was not possible to blind the study subjects or those measuring the outcomes due to the nature of the intervention.
The study provided estimates of the random variability in the data for the main outcomes (standard deviation provided).	It was not clear whether the analyses were adjusted for different lengths of follow-up.
All adverse events that could have been of consequence were reported.	There was no power calculation reported.
There were no losses to follow-up.	It was not possible to randomize subjects, or conceal the intervention assignment.
No unplanned subgroup analyses were reported.	
The statistical tests used to assess the main outcomes were not described but seemed appropriate.	
The main outcome measures used were valid and reliable, although no formal classification system used to grade infection was provided or described.	
Muderis 2016[13]	
The objective of the study was described.	The main outcomes to be measured were not clearly described

Strengths	Limitations
	in the introduction or results (except adverse events).
The characteristics of the included patients were clearly described.	It is not known whether the participants in the study were representative of the entire population from which they were recruited. The study inclusion criteria require participants to experience socket prosthesis issues, which impacts generalizability and could potentially overestimate the effect of the intervention. Patients with diabetes, vascular disease, and psychological disorder were excluded, impacting generalizability.
The intervention of interest was clearly described.	It is not possible to determine whether the subjects who were prepared to participate were representative of the population from which they were recruited.
The main findings of the study are clearly described.	It is not possible to determine whether the staff, places and facilities where the patients were treated are representative of the treatment the majority of patients receive.
The study provided estimates of the random variability in the data for the main outcomes (standard deviation provided).	t was not possible to blind the study subjects or those measuring the outcomes due to the nature of the intervention.
All adverse events that could have been of consequence were reported.	It was not clear whether the analyses were adjusted for different lengths of follow-up.
The authors stated that no patients were lost to follow-up.	It was not possible to randomize subjects, or conceal the intervention assignment.
Probability values reported are < 0.001	There was no power calculation reported.
No unplanned subgroup analyses were reported.	
The statistical tests used to assess the main outcomes appeared to be appropriate.	
The main outcome measures used were valid and reliable, although no formal classification system used to grade infection was provided or described.	
Muderis 2016[7]	
The objective of the study was described to a satisfactory degree.	Actual probability values were not reported.
The outcomes were clearly described in the methods section.	It is not known whether the participants in the study were representative of the entire population from which they were recruited.. The study inclusion criteria require participants to experience socket prosthesis issues, which impacts generalizability and could potentially overestimate the effect of the intervention. Patients with diabetes, vascular disease, and mental illness were excluded, impacting generalizability.
Patient characteristics were clearly described.	It is not possible to determine whether the subjects who were prepared to participate were representative of the population from which they were recruited.
The intervention was clearly described.	The intervention was undertaken at a specialized orthopedic osseointegration clinic; It is not possible to determine whether the staff, places and facilities where the patients were treated are representative of the treatment the majority of patients receive.

Strengths	Limitations
The main findings of the study were clearly described.	It is not possible to blind study subjects or those measuring outcomes due to the nature of the intervention.
Standard deviation and confidence intervals were reported.	It was not clear whether the analyses were adjusted for different lengths of follow-up.
All important adverse events that could be of consequence were reported.	It was not possible to randomize subjects, or conceal the intervention assignment since there was not a comparison group.
There were no patients lost to follow-up.	There was no power calculation reported.
No unplanned subgroup analyses were reported.	
The statistical tests used to assess the main outcomes appeared to be appropriate.	
The main outcome measures used were valid and reliable, although no formal classification system used to grade infection was provided or described.	
Haggstrom, 2013[17]	
The objective of the study was clearly described.	It is not known whether the participants in the study were representative of the entire population from which they were recruited. However, participants with amputations caused by diabetes or arteriosclerosis, were excluded, impacting generalizability.
The main outcomes to be measured were described in the Methods section.	It is not possible to determine whether the subjects who were prepared to participate were representative of the population from which they were recruited.
Patient characteristics were clearly described.	It is not possible to determine whether the staff, places and facilities where the patients were treated are representative of the treatment the majority of patients receive.
The intervention of interest were clearly described, although no etails was provided on the OIP procedure.	It does not appear that the control group and study group were recruited from the same population.
Distributions of potential confounders were clearly described, and potential confounding (due to sex ratio and different types of prosthetic equipment) was discussed and considered unlikely.	The subjects in each group were not recruited over the same period of time. The control group was selected from a previous study in 2004)
The main findings were clearly described.	Study subjects were not randomized, nor was blinding, or concealment.
Estimates of random variability including standard deviation are provided.	There was no power calculation reported.
No patients were lost to follow-up.	
Actual probability values were reported.	
The statistical tests used to assess the main outcomes appeared to be appropriate.	
There were no compliance issues.	
There were no unplanned subgroup analyses.	
Follow-up was the same for all participants.	

Strengths	Limitations
The main outcome measure used was valid and reliable.	

Table A8: Strengths and Limitations of Guidelines using AGREE II

Strengths	Limitations
National Institute for Health and Care Excellence [18]	
The overall objective of the guideline was specifically described.	It was not clear whether the guideline development group included individuals from all relevant professional groups.
The health question covered by the guideline was specifically described.	The criteria for selecting the evidence were not clearly described.
The population to whom the guideline is meant to apply was specifically described.	The strengths and limitations of the body of evidence were not clearly described, although some limitations were briefly discussed.
The views and preferences of the target population (patients, public, etc.) was sought via a public comment period.	No procedure for updating the guideline was provided.
The target users of the guideline were clearly defined.	Competing interests of guideline development group members were not recorded and addressed.
Systematic methods were used to search for evidence.	The guideline does not describe facilitators and barriers to its application.
The methods for formulating the recommendations are clearly described (at the NICE website).	No statement was made regarding the views of the funding body having not influenced the content of the guideline.
The health benefits, side effects, and risks were considered in formulating the recommendations.	
There is an explicit link between the recommendations and the supporting evidence.	
The guideline was externally reviewed by experts prior to its publication.	
The recommendations are specific and unambiguous.	
The different options for management of the condition or health issue are clearly presented.	
Key recommendations are easily identifiable.	
The guideline provides advice and/or tools on how the recommendations can be put into practice.	
20. The potential resource implications of applying the recommendations have been considered.	
The guideline presents monitoring and/or auditing criteria.	

Appendix 5: Main Study Findings and Author's Conclusions

Table A9: Summary of Findings of Included Systematic Reviews

Main Study Findings	Author's Conclusion
Leijendekkers, 2019[4]	
Quality of Life n=5 low-quality cohort studies that utilized the Q-TFA and reported that condition-specific QoL improved significantly in the first and second years after OIP relative to socket prosthesis; n = 2 low-quality cohort studies utilized the SF-36 to report that general QoL scores improved significantly with the use of an OIP rather than a socket prosthesis across several subscales in the first and second years after intervention (physical functioning, role physical functioning, and physical component summary). However the physical bodily pain subscale did not change, nor did the physical general health or mental health subscales. N = 1 low-quality cohort study that utilized the SF-6D and reported an improvement in general health status in the second year after OIP relative to socket prosthesis. Function Level n= 3 low-quality cohort studies used the Q-TFA to assess prosthesis wearing time and reported that wearing time improved significantly with use of OIP rather than a socket prosthesis in the first and second year after OIP. N = 1 low-quality cross-sectional study compared range of hip motion and reported lower range of motion for socket prosthesis users, between 2 and 10 years after OIP. n = 1 low-quality cross-sectional study reported that OIP users had a gait more similar to healthy subjects than did socket users. Activity Level n = 3 low-quality cohort studies utilizing the Q-TFA reported significant improvements in overall mobility score, capability subscore, and walking habit subscore with the use of an OIP relative to a socket prosthesis, but no change in walking aid subscores, in the first and second years after surgery. n = 1 low-quality cross-sectional study reported significantly less discomfort when sitting in OIP users compared with socket prosthesis users. n = 1 low-quality cohort study reported that walking ability improved significantly in the first year after OIP surgery compared with socket prosthesis users. n = 2 low-quality cohort studies found that the use of an OIP reduced the energy cost of walking significantly relative to socket prosthesis users in the first and second years following surgery.	"We found limited evidence that in patients with a transfemoral amputation, use of a bone-anchored prosthesis increased condition-specific and general physical QoL compared with socket prosthesis use, and was associated with higher function and activity." (p. 12) "...there is consensus in how to evaluate QoL; however, there is little consistency in the instruments used to evaluate function, activity, and participation level." (p. 12)

Main Study Findings	Author's Conclusion
Participation Level n = 1 low-quality cohort study found no evidence that work situation was different two years after OIP surgery compared with before surgery	
Van Eck, 2015[18}	
Prosthetic Use N = 5 studies reported 82% to 90% of patients used their OIP daily (noncomparative data). N = 1 study reported 14 hours of use per day compared with 8 hours for a socket prosthesis. Quality of Life (SF-36) N = 3 studies reported satisfactory SF-36 scores (no comparator), comparative data reported for n=1, reporting significant improvement at 2-year follow-up. Prosthetic Use, Mobility, Problems, and Global Health (Q-TFA) N = 4 studies reported Q-TFA scores, comparative data was reported for n=3 studies, with OIP patients reporting overall higher scores. Complications and Adverse Effects n = 3 studies, skin complications, 30% to 54% n = 2 studies, skin colonization, 4% to 44% n = 4 studies, skin infection, 28% to 55% n = 7 studies, implant infection, 2% to 41% n = 1 study, early infection, 16% n = 1 study, late infection, 25% n = 4 studies, implant loosening, 2% to 6% n = 3 studies, periprosthetic fracture, 0% to 9% n = 7 studies, revision surgery, 8% to 67% n = 9 studies, explant, 3% to 20% Patient Satisfaction n = 2 studies (possibly reporting on the same population) reported a 95% satisfaction rate. Radiostereometric Analysis n = 1 study reported average migration of the OPRA prosthesis by 0.17 mm on average; average rotation of the prosthesis = 0.38 degrees; cortical thinning and cancellization in all patients; trabecular streaming in 5%. Gait n = 1 study, sing the TUG test, participants with an OIP walked significantly further (27%) than socket prosthesis users, and were significantly faster (44%). Cost Analysis n = 1 study reported fewer office visits with an osseointegrated prosthesis compared with a socket prosthesis (3.1 visits versus 7.2 visits per year). The mean total annual cost of new prosthesis was 14% lower for an osseointegrated prosthesis (€ 3149 versus	"...an osseointegrated prosthesis resulted in a good quality of life and patient reported outcome. It also showed a considerable complication rate, specifically for skin problems, skin infection, implant infection and revision surgery. Patients were generally satisfied with the osseointegrated prosthesis, and most of them used the prosthesis on a daily basis." (p. 357)

Main Study Findings	Author’s Conclusion
€ 3672). Material costs for an osseointegrated prosthesis are higher, making the annual costs of both types of prostheses similar. <u>Oxygen Consumption</u> n = 1 study reported significantly less oxygen consumption (18%) in OIP compared with socket prosthesis users.	

6MWT = Six Minute Walk Test; OIP = osseointegrated prosthesis; OPL = Osseointegrated Prosthetic Limb; Q-TFA = Questionnaire for Persons with a Transfemoral Amputation; QoL = Quality of Life; SF-36 = Short Form (36) Health Survey; TUG = Timed Up and Go

Table A10: Summary of Findings of Included Studies

Main Study Findings	Author’s Conclusion
Muderis, 2017[6]	
Qol: Q-TFA Scores = approximately 42 for socket prosthesis versus 78 for OIP (approximate figures taken from bar graph, *P* <0.05) SF-36 physical component summary = approximately 36 for socket prosthesis versus 48 for OIP (approximate figures taken from bar graph, *P* <0.05) Functon: 6MWT: Mean increase of 128% over baseline (*P* < 0.05) TUG: Mean reduction of 30% (*P* < 0.05). Adverse events: Infection: Total: 15 cases in 12 patients; Grade 1 infection: 12 cases in 10 patients (treated with oral antibiotics); Grade 2 infection (treated with intravenous antibiotics): 3 cases in 12 patients. Refashioning surgery (elective soft-tissue refashioning), n = 6 Death not due to intervention, n = 1	*“...osseointegration surgery using the OPL implant is a relatively safe and effective procedure for the reconstruction and rehabilitation of lower limb amputees. Short-term clinical outcomes showed significant improvements in post-operative quality of life and function, which were associated with a low risk of severe adverse events.” p. 5*
Muderis, 2016[13]	
SF-36 Mean pre-operative: 37.09 (SD: 9.54) Mean post-operative: 47.29 (SD: 9.33) *P* <0.001 <u>Q-TFA</u> Mean pre-operative: 47.82 (SD: 17.28) Mean post-operative: 83.52 (SD: 18.04) *P* < 0.001 <u>TUG</u> Wheelchair-bound (n = 14/50): Mean pre-operative: NR Mean post-operative: 9.0 seconds	*“These results demonstrate that osseointegrated prostheses are a suitable alternative to socket-fit devices for amputees experiencing socket-related discomfort and that our strategy offers more rapid progress to walking than other similar protocols. (p. 952)* *Surgical conversion from a standard socket-style mounting of prosthetic limbs to an osseointegrated reconstruction with a press-fit implant consistently resulted in clinically significant improvements in patient satisfaction, quality of life and functional ability. (p. 959)*

Main Study Findings	Author's Conclusion
Prosthetic user (n = 36/50): Mean pre-operative: 14.59 seconds (SD: 5.94) Mean post-operative: 8.74 seconds (SD 2.81) *P* < 0.01 6MWT Wheelchair-bound (n = 14/50): Mean pre-operative: NR Mean post-operative: 411 metres (SD: 5.94) Prosthetic user (n = 36/50): Mean pre-operative: 281 metres (SD: 93) Mean post-operative: 410 metres (SD: 133) *P* < 0.001 AMPRO K-levels (measure of ambulatory ability or potential) improved in n = 30 patients, and were unchanged in n = 20 patients (*P* = 0.001) Adverse Events Total adverse events, n = 27 Soft tissue refashioning (to avoid impingement, skin irritation, and infection): n = 10 Infections: n = 21 patients experienced one or more infections (n = 13 responded to oral antibiotics, n = 5 responded to intravenous antibiotics, n = 3 required soft-tissue debridement) Peri-prosthetic fractures: n = 4 (previously wheelchair bound with severe osteoporosis) Implant revision: n = 2 (one due to failure of osseointegration attributed to an undersized implant, one due to implant fatigue failure at 3.5 years)	
Muderis, 2016[7]	
Adverse events Infection Total: n = 29 patients with 47 events Grade 1 infection: n = 25 Grade 2 infection: n = 4 Other Stoma hypergranulation: n = 17 patients (22 events) Redundant soft tissue: n = 14 patients (23 events) Proximal femoral fracture: n = 3 Inadequate osseointegration with replacement of implant: n = 1 Breakage of intramedullary component: n = 2 Breakage of pin used for safety: n = 25 patients (30 events) Significant Risk Factors (*P* < 0.05) Association of female sex with severe infection: OR, 6.5 [95% CI, 1.1 to 38.15]	*"In conclusion, this multicenter prospective cohort study indicates that severe infections resulting in septic implant loosening are rare. Mild infection and irritation of the soft tissue in the skin penetration area are common; these complications can be managed with simple measures. Protocols for adequate surgical management of the peri-implant soft tissue are essential." (p. 908)* *"The fact that smoking and female sex were associated with recurrent infection and severe infection requiring surgery, respectively, suggests that they are useful criteria for patient counseling and selection." (p. 907)*

Main Study Findings	Author’s Conclusion
Association of smoking with recurrent infection: OR, 7.5 [95% CI, 1.32 to 42.35] Association of BMI > 25 kg/m^2 with mild infection: OR, 3.47 [95% CI, 1.16 to 10.39]	
Haggstrom, 2013[17]	
The OIP group had significantly improved ability to detect vibrations through the prosthesis at 125 Hz (p =0.01) at follow-up compared with the preoperative measurement The OIP group at follow-up had better ability to detect high frequency vibrations through the prosthesis (125 Hz, p = 0.02; 250 Hz, p = 0.03) compared with the control group.	The results of this study showed that patients with TFA using OI prostheses have an improved detection threshold for high-frequency vibratory stimulations applied under the prosthetic foot.” “Feedback of high frequency vibrations from the surroundings through the prosthetic components have in this study been shown to be more easily recognized by patients treated with OI amputation prostheses as compared with conventional socket prostheses, potentially leading to advantages in gait control for patients with an OI prosthesis.” (p. 1431)

6MWT = Six Minute Walk Test; AMPRO = Amputation Mobility Predictor; BMD = bone mineral density; BMI = body mass index; CI = confidencd interval; CT = computed tomography; ILP = Integral Leg Prosthesis; OI = osseointegrated; OIP = osseointegrated prosthesis; OGAAP-1 = Osseointegration Group of Australia Accelerated Protocol; OPL = Osseointegrated Prosthetic Limb; Q-TFA = Questionnaire for Persons with a Transfemoral Amputation; QoL = Quality of Life; SF-36 = Short Form (36) Health Survey; TFA = transfemoral amputation; TUG = Timed Up and Go

Table A11: Summary of Findings of Included Guidelines

Recommendation	GRADE/Strength of Recommendation or Interpretation
National Institute for Health and Clinical Evidence(NICE)[9,18]	
The OIP procedure should only be used with special arrangements for clinical governance, consent and audit or research, since current evidence on the safety and efficacy of this procedure is inadequate in quantity and there is a lack of long-term follow-up Clinicians wishing to undertake OIP should 1) inform the clinical governance leads in their Trusts, 2) ensure that potential patients understand the uncertainty about the procedure's safety and efficacy, in particular with regard to the longer term, and provide them with clear written information, and 3) audit and review clinical outcomes of all patients an OIP Patient selection should be carried out by a multidisciplinary team: a surgeon experienced in amputation and in the necessary bone and soft tissue reconstruction, and rehabilitation specialists, including experts in prosthetics and implant design Clinicians are encouraged to collaborate in the collection and publication of data, particularly in relation to adverse events such as infection and long-term performance of the implants.	The guidance was informed by two non-randomized comparative studies, three case series, and specialist opinion. No formal grading of evidence was attempted.

OIP = Osseointegrated prosthesis

Appendix 6: Additional References of Potential Interest

Abstracts/Conference Proceedings

Aschoff, H. Evaluation of 10 years of experience with endo-exo-prostheses: Highlights and pitfalls of osseointegration, transcutaneous implants for rehabilitation of amputees. In: *2012 Orthopaedic Surgical Osseointegration Society 4th International Advances in Orthopaedic Osseointegration Conference Syllabus Abstracts*. Orthopaedic Surgical Osseointegration Society: San Francisco, CA

Khemka A, Frossard L, Lord S, Bosley B, Al Muderis M. Health-related quality of life of individuals with transfemoral amputation fitted with the Transcutaneous Bone Anchoring Prosthesis following the OGAAP. 2015. http://eprints.qut.edu.au/89029/1/Abs-ISPO%20Lyon-AK-ILP%20and%20QTFA-ePrint%2001.pdf

Rubin L, Kennon R, Keggi J, Aschoff H-H. Surgical management of trans-femoral amputations wtih a transcutaneous, press-fit distal femoral intra-medullary device: Analysis with minimum 2-year follow-up. http://www.bjjprocs.boneandjoint.org.uk/content/94-B/SUPP_XXI/95

Case Series

Lenneras M, Tsikandylakis G, Trobos M, Omar O, Vazirisani F, Palmquist A, et al. The clinical, radiological, microbiological, and molecular profile of the skin-penetration site of transfemoral amputees treated with bone-anchored prostheses. J Biomed Mater Res A. 2017 Feb;105(2):578-89. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5216444

Vertriest S, Coorevits P, Hagberg K, Branemark R, Haggstrom EE, Vanderstraeten G, et al. Static load bearing exercises of individuals with transfemoral amputation fitted with an osseointegrated implant: Loading compliance. Prosthet Orthot Int. 2016 Apr 26.

Costs

Burkett B, Frossard LA, Berg D, Formosa D. The cost and time effectiveness of osseointegration compared to the traditional socket prosthesis. 2014. http://eprints.qut.edu.au/84787/1/2014%20Abs-USC-Research%20Week-ePrint%2001.pdf

Frossard LA. Merlo G, Quincey T, Berg D, Burkett, C. Cost-effectiveness of bone-anchored prosthesis: the Queensland experience. In Australian Orthotic Prosthetic Association (AOPA) Congress, 25 September 2015, Adelaide, S.A. http://eprints.qut.edu.au/87958/1/Abs-AOPA%20conf-Adelaide-Cost-effectiveness%20and%20QLD%20experience-ePrint-ALL-V01.pdf

Ongoing Clinical Trials

Osseointegrated Prostheses for the Rehabilitation of Amputees [ongoing clinical trial]. Study start date: May 1999. Estimated study completion date: May 2027. https://clinicaltrials.gov/ct2/show/NCT01725711

Surveys

Webster JB, Chou T, Kenly M, English M, Roberts TL, Bloebaum RD. Perceptions and acceptance of osseointegration among individuals with lower limb amputations: A prospective survey study. 2009. http://www.oandp.org/jpo/library/2009_04_215.asp

Lundberg M, Hagberg K, Bullington J. My prosthesis as a part of me: a qualitative analysis of living with an osseointegrated prosthetic limb. Prosthet Orthot Int. 2011 Jun;35(2):207-

Protocols

Leijendekkers RA, Staal JB, van HG, Frolke JP, van de MH, Atsma F, et al. Long-term outcomes following lower extremity press-fit bone-anchored prosthesis surgery: a 5-year longitudinal study protocol. BMC Musculoskelet Disord. 2016 Nov 22;17(1):484. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5120460